REMARKS

The Applicants respectfully rebut the Examiner's argument that Claims 1-7 are obvious in light of Watson & Bennett (Biotechniques, 1997), Liu (Current Biology, 1998) and Stahl (Biotechniques, 1993).

A. References do not teach "removing and circularizing"

According to MPEP §2143, to establish a prima facie case of obviousness the prior art references when combined must teach or suggest **all** the claim limitations.

The combined references **do not** teach the added benefit of circularizing and releasing the assembled DNA in a **single event** by recombination. Watson & Bennett (also repeated within the present specification as example 1) teach the assembly of PCR fragments. Liu teaches the fusion and circularization of a plasmids using CRE-*lox*. Finally Stahl teaches the synthesis of a gene on solid support. Although each of these references teach some elements of the claimed invention, none teach "**removing and circularizing** the assembled fragment from the solid support with a site specific recombinase." This single-step removal and circularization is clearly novel and beneficial.

B. Impermissible Hindsight

Applicants argue the combination of two or more references is "hindsight" because "express" motivation to combine the references is lacking. According to MPEP §2143.01 The level of skill in the art cannot be relied upon to provide the suggestion to combine references. *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999). Motivation to combine must come from the nature of the problem to be solved, the teachings of the prior art, and the knowledge of persons of ordinary skill in the art." *In re Rouffet*, 149 F.3d 1350, 1357, 47 USPQ2d 1453, 1457-58 (Fed. Cir. 1998).

The nature of the problem to be solved: "**removing and circularizing** the assembled fragment from the solid support with a site specific recombinase."

Although the level of skill in the art is high, there is no motivation to combine the references. Watson and Bennett are one example of the level of skill at the time the application was filed. Watson and Bennett teach assembly of PCR fragments using DNA repair enzymes to generate 3'

overhangs in 2 or more DNA fragments and ligating the fragments. Further Watson and Bennett teach circularization of the assembled DNA *in vivo* using CRE-*lox*. Watson and Bennet **fail to teach** the single-step removal and circularization of the assembled fragment from the solid support.

Liu, *et al.* teach a series of plasmid cassettes (both circular) which can be used to insert a protein cassette into various plasmids depending on host and plasmid function (i.e. protein expression, high copy plasmid, or various host strains). When Liu, *et al.* teach the "UPS eliminates the use of restriction enzymes and DNA ligase…" They refer to the complex steps required for moving protein cassettes from one vector to another. These cloning procedures are **not related** to the assembly of DNA fragments *in vitro* using the present invention. Liu, *et al.* **fail to teach** the single-step removal and circularization of linear DNA to form a plasmid.

Stahl, *et al.* teach the assembly of DNA fragments on a solid support. The method is taught to increase accuracy and size of synthesized DNA or oligos. Traditionally oligo size is limited by the error rate of DNA synthesis and drops dramatically as you approach 100 nt in length. In order to increase the length above 100 nt, Stahl, *et al.* propose fixing the oligos to a solid support and adding sequential lengths of synthetic DNA. Stahl, *et al.* does not comtemplate assembly of an entire plasmid or PCR fragments on a solid support and is **not related** to the present invention. Stahl, *et al.*, **fail to teach** the single-step removal and circularization of linear DNA to form a plasmid.

As described above, the selected references present three very different problems to be solved using different technologies. It is improper hindsight to combine these references to generate a plasmid (Watson and Bennett), interchangeable plasmid cassettes (Liu, *et al.*) and oligo synthesis (Stahl, *et al.*). They are **unrelated** and therefore should not be combined.

CONCLUSION

The removal and circularization of the linear PCR fragments provides a powerful tool for biological applications. Using the methods described in the present application, a person of ordinary skill in the art may construct a custom DNA sequence using a series of PCR reactions, assemble the PCR products on a solid support, and **in a single step** using a site specific recombinase remove and circularize a product that is ready for transformation into cells. The

cited references do not establish a *prima facie* case of obviousness (MPEP §2143) because there is no suggestion or motivation to combine these **unrelated references** and the combined references **fail to teach** or suggest "**removing and circularizing** the assembled fragment from the solid support with a site specific recombinase."

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to pass this application to issue. The Applicants respectfully request the Examiner contact them if there are any questions or procedures that need to be addressed. No fees are believed to be due for this submission. However, should there be any additional fees required, please charge such additional fees to Deposit Account No. 50-3420 (reference 31175413-002002 MDB).

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Respectfully submitted,

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